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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,955	10/31/2003	Edward A. Neuwelt	720109.404	8802

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EXAMINER	
CHOI, FRANK I	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,955	NEUWELT ET AL.	
	Examiner	Art Unit	
	Frank I. Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5,7,14-22,29 are rejected under 35 U.S.C. 102(b) as being anticipated by Neuwelt et al. (Reference CK in PTO-1449 (7/15/2005)).

Neuwelt et al. expressly disclose the amelioration of decrease in platelets due to carboplatin, etoposide phosphate and melphalan treatment of brain and non-brain cancer, using N-acetylcysteine with or without sodium thiosulfate, post and/or prior to chemotherapy, with or without blood brain barrier disruption (Pgs. 7868-7871) .

The Examiner has duly considered Applicant's arguments but deems them unpersuasive.

Since the rejection herein is under 102(b), the affidavit provided indicating that the relevant disclosure in the reference was derived from the inventor is not applicable.

Applicant argues that the 102(b) rejection is not applicable because of a priority date based on a provisional application filed on 10/31/ 2002. The present non-provisional application was filed on 10/31/2003, which is more than a year after the publication of the reference cite above. In order for the claims herein to gain benefit of the earlier priority date, the provisional

application must provide support for the full scope of said claims pursuant to 35 USC 112, 1st paragraph, i.e. both written disclosure and enablement. In this case, the provisional application does not enable the full scope of the claims and/or provide written description support for the claims because the subject matter of the claims are broader in scope than the disclosure of the provisional application as follows: The only chemotherapeutic agents disclosed are carboplatin, cisplatin, cyclophosphamide, etoposide and G-CSF. The only working example (example 2 is prophetic example) provided is with respect to sodium thiosulfate and a combination of carboplatin, cyclophosphamide and etoposide, however, the sodium thiosulfate was only dosed in relation to the carboplatin. The example showed percent decrease in the incidence of thrombocytopenia but does not provide support for the full scope of the claim, including prevention or amelioration of thrombocytopenia due to any chemotherapeutic agent with any thiol-based compound or that administration of the same would completely prevent the patient from ever having chemotherapeutic agent induced thrombocytopenia. N-acetylcysteine was disclosed but not used in an example. With respect to specific limitations in the dependent claims, there does not appear to a disclosure of intra-arterial administration as claimed in claim 4, the administration of a thiol-based compound prior to the administration of the chemotherapeutic agent or agents as claimed in claim 5 (the only administration disclosed is 4 hours or 4 and 8 hours after carboplatin), the use of other thiol-based compounds as claimed in claim 14, any alkylating agent or platinum-containing alkylating agent as claimed in claims 18, 19, respectively, oxyplatin as claimed in claim 20, or the treatment of a patient that has a cancer other than brain tumor (the disclosure appears only to disclose treatment of patients having brain tumors) as claimed in claim 29. In view of the prior art below, it appears that the prior art does not disclose much more than what is set forth in the provisional application. As such, it appears

that predictability in the art is low as to what other chemotherapeutic agents or combinations thereof cause thrombocytopenia, which other thiol-based compounds would be effective for preventing or ameliorating thrombocytopenia in a given chemotherapeutic agent or combinations thereof and which other chemotherapeutic agents or combinations thereof would be susceptible to the action of sodium thiosulfate or acetylcysteine. As such, it appears that one of ordinary skill in the art would be required to do undue experimentation in order to determine what other chemotherapeutic agents or combinations thereof cause thrombocytopenia and determine what thiol-based compounds, doses and routes of administration would be effective in preventing or ameliorating the same.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being obvious over Neuwelt et al. (Reference CK) in view of Muldoon et al. (Reference CH) and Doolittle et al. (Blood (November 2001)).

Neuwelt et al. discloses the amelioration of decrease in platelets due to carboplatin, etoposide phosphate and melphalan treatment of brain and non-brain cancer, using N-acetylcysteine with or without sodium thiosulfate, post and/or prior to chemotherapy, with or without blood brain barrier disruption (Pgs. 7868-7871). It is disclosed that after osmotic blood brain barrier disruption (BBBD), sodium thiosulfate administration must be delayed at least 60 minutes when the blood brain barrier is reestablished or seizures result (Pg. 7872). It is disclosed that recent data suggests that delayed sodium thiosulfate may provide platelet protection in brain tumor patients (Pg. 7871).

Muldoon et al. discloses that sodium thiosulfate, N-acetylcysteine and glutathione ethyl ester act as chemoprotectants against toxicity of carboplatin, cisplatin, etoposide phosphate and melphalan, with maximally effective protection against melphalan toxicity occurring if

administered concurrently, whereas chemoprotection for the platinum agents remained effective if delayed at least 4 hours (Pgs. 797-803). It is disclosed that chemoprotection with sodium thiosulfate did not reduce the efficacy of carboplatin if administration was delayed for 8 hours after chemotherapy (Pg. 804). It is disclosed that sodium thiosulfate may be safely administered in single bolus doses up to 20 g/m2 (Pg. 803).

Doolittle et al. discloses that delayed administration of 16-20 gm/m2, based on blood/bone marrow toxicity data, may protect against severe thrombocytopenia inpatients treated with a caboplatin-based BBBD regimen in which cyclophosphamide, etoposide or etoposide phosphate, and G-CSF were part of the regimen (Abstract).

The prior art discloses protecting against thrombocytopenia induced by the disclosed chemotherapeutic agents with acetylcystine with or without sodium thiosulfate. The difference between the prior art and the claimed invention is that the prior art does not explicitly disclose a method of ameliorating thrombocytopenia induced by chemotherapy where the administration of the active agent is concurrent, delayed for at least 30 minutes, or used to treatment in humans. However, the prior art amply suggests the same treatment of animals with N-acetylcysteine or sodium thiosulfate has been effective in protecting platelets from chemotherapy toxicity, including pre and post administration, sodium thiosulfate should be administered at least 60 minutes after BBBD. As such, it would have been well within the skill of and one of ordinary skill in the art would have expected that concurrent administration would also be effective, that administration at least 30 minutes or more would also be effective and that disclosed methods would also be effective in ameliorating/preventing decrease in platelets in humans.

The Examiner has duly considered Applicant's arguments but deems them unpersuasive for the same reasons above and the further reasons below. In addition to the above, the

provisional application does not appear to disclose the concurrent administration of any thiol-based compound with any chemotherapeutic agent or agents as claimed in claim 6, the ranges of time post administration of the chemotherapeutic agent or agents when the thiol-based compound is administered as claimed in claims 8-13, 28, and the dosage of 15 grams of sodium thiosulfate as claimed in claim 27. Therefore, as indicated above, the claims are not entitled to the priority date of 10/31/2002 since the provisional application does not support the claim limitations pursuant to 35 USC 112, 1st paragraph. As such, since the actual filing date of the present non-provisional application of 10/31/2003 is more than a year after the publication of the Doolittle et al. and Neuwelt references, the 103(a) obviousness rejection with respect to said references is based on the use of said references as 102(b) references not 102(a) references. For the same reasons, the affidavits provided indicating that the relevant disclosure in said references was derived from the inventor are not applicable.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a compressed schedule and may be reached Monday, Tuesday, Thursday, Friday, 6:00 am – 4:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Dr. Johann Richter, can be reached at (571)272-0646. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frank Choi
Patent Examiner
Technology Center 1600
September 8, 20063